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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for 1, 2-Diphenylhydrazine.

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Prepared for

OFFICE OF WATER REGULATIONS
AND STANDARDS

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
RQ	Reportable quantity
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on diphenylhydrazine, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1986 to 1988 for 1,2-diphenylhydrazine and in 1980 to 1988 for 1,1-diphenylhydrazine). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

No new pertinent data for 1,1-diphenylhydrazine or 1,2-diphenylhydrazine were located in the available literature. The AWQCD (U.S. EPA, 1980) did not report any data on toxicologic or carcinogenic effects of the 1,1-isomer.

U.S. EPA (1980) recommended criteria for diphenylhydrazine based on the results from an NCI (1978) study in which 6-week-old Fischer 344 rats and B6C3F1 mice were given technical grade 1,2-diphenylhydrazine (K&K Labs) in the diet for 78 weeks and observed for an additional 28 and 18 weeks, respectively. Rats were divided into four experimental groups of 50 animals each: high-dose males, low-dose males, high-dose females and low-dose females. Each of these groups had its own control group. Mice were divided in a similar manner. The TWA dietary concentrations were 0.008 and 0.03% for male rats, 0.004 and 0.01% for female rats, 0.008 and 0.04% for male mice, and 0.004 and 0.04% for female mice. Variables monitored were mortality, body weight, food consumption and histopathology of all major organs and tissues. Survival rate was not affected in male rats, but high-dose female rats had a significantly higher mortality than controls. A slight reduction in body weight gain was noted in high-dose male and female rats.

Treated male rats showed a significant increase in the incidence of hepatocellular carcinomas (both doses), whereas treated high-dose females exhibited an increased incidence of neoplastic nodules of the liver and mammary adenocarcinomas. Also, high-dose male rats showed a significant increase in the combined incidence of squamous-cell carcinomas or squamous-cell papillomas of the Zymbal gland, the ear canal or the skin of the ear. Body weight gain was not affected in male or female mice; however,

mortality was increased in both high-dose groups. Moreover, female mice showed a significant dose-related increase in the incidence of hepatocellular carcinomas. After analyzing the results, NCI (1978) concluded that under the experimental conditions used, 1,2-diphenylhydrazine was carcinogenic to male and female Fischer 344 rats and to female B6C3F1 mice.

The results described above are supported by an earlier study by Pliss (1974) in which 1,2-diphenylhydrazine in sunflower oil was given to rats and mice for 588 days either mixed into the diet (30 mg/5 times/week), by topical application to the skin (2 mg/3 times/week/mouse) or by subcutaneous injection (40 mg/week/rat; 5 mg/week/mouse). Approximately 50% of all treated mice and 22% of the rats developed tumors. Since some control data were missing and animals were added during the course of the experiment, this study provides only qualitative evidence of carcinogenicity for 1,2-diphenylhydrazine.

In a report by Maronpot et al. (1983) examining the strain A mouse pulmonary tumor bioassay model to predict the potential carcinogenicity of chemicals, 1,2-diphenylhydrazine was one of 60 chemicals submitted for testing and comparison to NTP bioassay data. In this study, 1,2-diphenylhydrazine was administered intraperitoneally 3 times/week for 8 weeks at various doses at/or approximating the maximum tolerated dose determined by the testing laboratory (exact doses not stated). Mice were sacrificed 16 weeks after the cessation of treatment and all grossly visible pulmonary tumors were counted. In this bioassay 1,2-diphenylhydrazine had a statistically significant increase ($p \leq 0.05$) in tumor incidence in treated versus vehicle controls. Since neither the doses or the tumor incidences were provided, this study provides only qualitative evidence of carcinogenicity for 1,2-diphenylhydrazine.

Based on the results available from studies in both rats and mice, 1,2-diphenylhydrazine has been classified as U.S. EPA Group B2: probable human carcinogen (U.S. EPA, 1986).

Bioconcentration Factor (BCF)

Pertinent new data concerning the bioconcentration factor for 1,2-diphenylhydrazine are currently undergoing Agency review. The BCF value of 24.9 determined in U.S. EPA (1980) will be used until this review is complete.

QUANTIFICATION OF EFFECTS

U.S. EPA (1980) recommended criteria for 1,2-diphenylhydrazine based on the study conducted by NCI (1978) (see previous section) in which male and female Fischer 344 rats and female B6C3F1 mice developed hepatocellular carcinomas and neoplastic nodules when exposed for 78 weeks to 1,2-diphenylhydrazine in the diet. From that study, a slope factor (q_1^*) of 0.768 $(mg/kg/day)^{-1}$ was calculated; this value, rounded to 0.8 $(mg/kg/day)^{-1}$, has been verified by CRAVE (U.S. EPA, 1986). The drinking water unit risk factor is 2.2×10^{-5} $(\mu g/\ell)^{-1}$. In the absence of new pertinent data, the derivation of criteria for ambient water remains the same as in U.S. EPA (1980).

Using the verified slope factor (q_1^*) of 0.768 $(mg/kg/day)^{-1}$ and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and shellfish with a BCF for 1,2-diphenylhydrazine of 24.9, the criteria for 1,2-diphenylhydrazine in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	4.2	42	422	4,220
Consumption of fish and shellfish only	0	56	560	5600	56,000

EXISTING STANDARDS AND CRITERIA

The U.S. EPA (1986) verified a slope factor (q_1^*) of 0.8 $(mg/kg/day)^{-1}$ for oral (see previous section) and inhalation exposure to 1,2-diphenylhydrazine based on the NCI (1978) oral exposure study in which male Fischer 344 rats developed hepatocellular carcinomas. The inhalation unit risk factor is 2.2×10^{-4} $(\mu g/m^3)^{-1}$.

CRAVE has verified the classification of 1,2-diphenylhydrazine in Group B2: probable human carcinogen (U.S. EPA, 1986).

An RQ of 10 pounds is proposed for diphenylhydrazine, based on aquatic toxicity and carcinogenicity (U.S. EPA, 1988).

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